REMARKS

Status of the specification.

Applicants present amendments to paragraphs of the specification as set forth above.

Status of the Sequence Listing.

The Office Action identified alleged deficiencies in the specification at p. 48. line 32 and p.49 line 1. Applicants note that the above deficiencies were previously corrected on page 2 of a Preliminary Amendment mailed on October 4, 2001 (Paper #8). Applicants faxed a copy of this page (enclosed) to the Examiner on January 8, 2003.

Status of the Information Disclosure Statements.

The Supplemental Information Disclosure Statement filed on October 9, 2001 was objected to as allegedly not providing the four references cited therein. Applicants submitted on May 19, 2003 a supplemental Information Disclosure Statement providing those four references. The Supplemental Information Disclosure Statement further lists additional references included in the file wrapper of U.S. Patent No. 6,303,573, a patent reference which concerns closely related subject matter.

Status of the Claims.

Claims 1-7, 28 and 29 were pending. Amendments are presented for claims 1, 3 and 6. Claim 30-35 are newly presented. After entry of these amendments, claims 1-7, and 28-35 would be pending.

Claims 1-7, 28 and 29 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not satisfying the written description requirement.

Claims 1-7, 28 and 29 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled.

Claims 1-4, 6-7, 28 and 29 stand rejected under 35 U.S.C. §102 as allegedly anticipated by Hall, et al. (U.S. Patent No. 6,387,663).

Claims 1-4, 6-7, 28 and 29 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Olson, et al., *International Journal of Cancer*, 73:865-70 (1997).

Claims 1-4, 6-7, 28 and 29 stand rejected under 35 U.S.C. §102 (b) as allegedly anticipated by Arora, et al., *Cancer Research*, 59:183-188, abstract only (1999).

Applicants respond to these rejections below.

Amendments to the Specification.

The first full paragraph on p. 18 was amended to correct a typographical error. The paragraph presented binding affinity data in units of $10^{x} M^{-1}$. One of ordinary skill in the art would readily recognize that the binding affinity data should have been presented as $10^{-x} M^{1}$.

The first paragraph on p. 27 was amended to recite the U.S. Patent Application and filing date previously identified according to Campbell & Flores LLP Attorney Docket # P-LJ 3512. Applicants enclose a copy of a paper from the file wrapper of the recited patent application which sets forth both the attorney docket number and the patent application serial number. Applicants also cite the corresponding issued patent on the Supplemental IDS, filed May 19, 2003. The recital of the serial number corresponding to the above attorney docket number was previously provided with the paragraph amendments submitted in the Sequence Listing.

Applicants believe the above amendments to the specification present no new matter and respectfully request their entry.

Amendments to the Claims.

Claims 1, 3 and 6 were amended to recite "targeting peptide". Support for such subject matter is found in the specification, *inter alia,* as set forth in the above amended

paragraph and in each of the Examples as well as in the definition of "molecule" in the first paragraph on p. 12.

Claim 1 was further amended to recite a "peptide angiogenic factor." Support for this subject matter is found in the specification, *inter alia,* at p. 6, line 15.

Claim 1 was further amended to recite "covalently linked." Support for this subject matter is found, *inter alia,* in the specification at p. 31, last paragraph and p. 49 Example 2.

Claim 3 was further amended and claim 31 was added to recite "the targeting peptide is selected from the group consisting of GGGVFWQ (SEQ ID NO:1), HGRVRPH (SEQ ID NO:2), VVLVTSS (SEQ ID NO:3), CLHRGNSC (SEQ ID NO:4), and CRSWNKADNRSC (SEQ ID NO:5)." Support for this subject matter is found, *inter alia,* in the specification in the first paragraph on p. 27 as originally filed and as amended herein.

New claim 30 recites "The chimeric molecule of claim 1, wherein the angiogenic factor is a VEGF homolog." Support for the subject matter of a VEGF homolog is found in the specification, *inter alia,* at p. 8, last full paragraph.

New claims 32-35 recite "A pharmaceutical composition comprising the chimeric molecule" of claim 2, 3, 4 or 30, respectively, "and a pharmaceutically acceptable carrier." Support for this subject matter is found, *inter alia,* in the original claim 28 and in the section titled "Formulation and Administration of Chimeric Molecules: Pharmaceutical Compositions" starting at p. 32 in the specification.

Applicants believe the above amendments present no new subject matter and respectfully request their entry.

Response to the Rejection of Claims 1-7, 28 and 29 as allegedly not satisfying the written description requirement.

In rejecting the claims, the Action stated:

> "The specification does not teach what is the complete structure of representative species of the genus. Except

> for disclosing that peptides are linked to VEGF and that the chimeric molecule is a fusion protein, the specification does not describe the structure of a representative number of species of the genus."

Without acquiescing to the position of the Examiner and in order to expedite prosecution of the application, the Applicants have amended the base claim to recite a "peptide angiogenic factor" and a "targeting peptide" in place of "an angiogenic factor" and a "targeting molecule," respectively. Claim 1, as amended, would now recite:

> A chimeric molecule comprising a peptide angiogenic factor covalently linked to a targeting peptide that specifically binds to a vascular endothelium.

Applicants respectfully disagree with the Examiner as to the number of species of angiogenic factors taught in the specification. In addition to a great many VEGF family members, the specification discloses a reasonable number of peptide angiogenic factors:

Placental growth factor family members

Fibroblast growth factor family members (20+)

Endostatin

Angiostatin

Angiopoietin family members

In view of the above, Applicants respectfully request that the above rejection be reconsidered and withdrawn.

Response to the Rejection of Claims 1-7, 28 and 29 as allegedly not enabled.

As noted by the Examiner, whether undue experimentation is required to practice an invention is typically determined by the Forman factors. These factors weigh (i) the relative skill of those in the art; (ii) the nature of the invention; (iii) the breadth of the claims; (iv) the amount of guidance presented; (v) the presence of working examples; (vi) the state of the art; (vii) the predictability of the art; and (viii) the quantity of

experimentation necessary. *Ex parte* Forman, 230 U.S.P.Q. 546 (PTO Bd. Pat. App. & Inter. 1986), *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988).

The Action rejected the above claims on the basis that

> the specification does not provide sufficient guidance as to how an artisan of skill would have made and used any claimed chimeric molecules for treatment and would have required extensive experimentation to make and use for the treatment and such experimentation would have been undue since neither the art nor the specification teaches treating any condition with the claimed chimeric molecules as discussed below and such experimentation was not routine in the art.

In framing the above rejection the Examiner pointed to several issues. Each will be addressed in turn. The first issue related to the breadth of the claims as related to the teachings of the specification:

> First, the issue is: is the specification enabling for making and using any chimeric molecule as recited in the claims? Except for teaching fusion proteins wherein an angiogenic factor protein is linked to a peptides, the specification does not provide any description for any other chimeric molecules. It is noted that an artisan would not have known how to make any chimeric molecule or what chimeric molecule in view of the lack of description of the chimeric molecules encompassed by the invention.

Applicants have noted the above comment and amended the base claim to recite a "peptide angiogenic factor" and a "targeting peptide" to more closely conform to the subject matter the Examiner considered to be disclosed. The base claim has also been further amended to recite "covalently linked." Methods for covalently linking the chimeric molecules include fusion proteins as acknowledged by the Examiner.

The base claim has not been further amended to recite a fusion protein as set forth in the dependent claim 6. The specification discloses more than fusion protein linkages in the specification. The specification also sets forth methods of chemically cross-linking the subject peptides using bifunctional cross linking reagents in Example 2 which teaches the use of carbodiimide and N-hydroxysuccinimide reagents. The art of protein cross-linking is a mature one and the specification incorporates by reference a standard text on

how to cross-link proteins. The specification further teaches in Example 3 how to extend the peptide chains with poly-Gly or poly-Ala sequences to reduce steric hindrance and interference between the subject peptides. The specification further teaches the use of spacer domains and heterobifunctional cross-linking groups in Example 4. Thus, Applicants believe that in view of the amendments to the specification and the teachings of the specification, the subject matter of covalently linking the subject angiogenic factor peptide and the targeting peptide is adequately enabled.

The Action was also concerned with the enablement of chimeric molecules for inducing angiogenesis *in vitro* or *in vivo*. In particular, the Examiner was generally concerned with a possible effect of the chimeric molecules moieties on each others' functionality. However, the three references cited by the Action as anticipating the claimed invention, put these concerns to rest: Hall, et al. teach that VEGF can be fused to collagen targeting peptides such as von Willebrand factor peptides without loss of either functionality. With respect to the issue of VEGF dimer formation and the biological activity of the conjugates, Hall, et al. teach that such conjugates do form dimers and retain their biological activity (*see*, for instance, Example 3, col. 19). Indeed Hall, et al. issued with the following broad claims:

> 1. A fusion polypeptide comprising:
>
> a) a collagen binding domain which binds exposed vascular collagen; and
>
> b) an angiogenesis modulating domain, wherein said angiogenesis modulating domain directly effects endothelial cell proliferation.
>
> 2. The fusion polypeptide of claim 1, wherein said collagen binding domain is a collagen binding domain of von Willebrand factor, or conservative variation thereof which retains collagen binding activity.
>
> 3. The fusion polypeptide of claim 2, wherein said collagen binding domain comprises the decapeptide Trp-Arg-Glu-Pro-Ser-Phe-Met-Ala-Leu-Ser (SEQ ID NO:1).
>
> 4. The fusion polypeptide of claim 1, wherein said

angiogenesis modulating domain is selected from the group consisting of a growth factor, growth factor (EGF), hepatocyte growth factor (HGF), platelet derived endothelial cell growth factor (PD-ECGF), platelet derived growth factor (PDGF); insulin-like growth factor (IGF), interleukin-8, growth hormone, angiopoietin, acidic and basic fibroblast growth factors (FGFs), transforming growth factor alpha (TGF-.alpha.), vascular endothelial growth factor (VEGF) an enzyme, an enzymatic inhibitor, and an antibody.

In addition, both Olson, et al. and Aurora, et al. disclose that VEGF binding activity is maintained even in the instance of VEGF covalent attachment to extremely large moieties. Olson, et al. teach that chemical conjugation of a VEGF peptide with a extremely large diphtheria toxin peptide 385 amino acids long results in a conjugate whose VEGF peptide retains its ability to interact with its endothelial receptor. Aurora, et al. teach that fusion of VEGF peptide to an extremely large diphtheria toxin peptide results in a fusion protein which retains the ability of VEGF to bind to its endothelial receptor.

The Examiner points out that the subject matter incorporated by reference and identified only by the Campbell and Flores attorney docket no. is not available to the skilled artisan. Applicants have addressed this deficiency by amending the relevant portion of the specification to recite the corresponding U.S. patent application serial number as well as the corresponding issued patent (U.S. Patent No. 6,303,573). Thus, this information will now be readily available to the skilled artisan.

With respect to the issue as to whether the chimeric molecule can specifically bind to the vascular epithelium, the subject matter of U.S. Patent No. 6,303,573, incorporated by reference in the present specification, broadly discloses and claims targeting peptides of the invention and that they target vascular endothelium of the heart and limbs (*see*, col. 4, lines 30-40 and col. 6, lines 19-33 for instance). The '573 patent further discloses in Examples 1 and 2 therein that such targeting peptides, when fused to phage proteins, can target a phage to vascular endothelium *in vivo*.

In view of the above, Applicants believe it would not require undue experimentation to practice the subject matter of a chimeric molecule of the claims combining a *functional* peptide angiogenic factor and a *functional* peptide targeting moiety.

The Examiner was also concerned as to the bioavailability and the pharmacokinetics of the chimeric molecule when administered by various routes. In this regard, it should be pointed out that the Examiner cites the Background for the proposition that "there is no indication that the current methods would promote the level of angiogenesis required to overcome peripheral or cardiac ischemias. Applicants set forth the full quoted paragraph below:

> Despite recent advances in identifying genes encoding ligands and receptors involved in angiogenesis, there is no indication that the current methods would promote the level of angiogenesis required to overcome peripheral or cardiac ischemias. For example, in existing therapy, there is the need for repeated or long term delivery of the angiogenic proteins to achieve an angiogenic effect. This can limit the utility of using these proteins to stimulate angiogenesis in clinical settings. In other words, successful therapy in humans would require sustained and long-term infusion of one or more of these angiogenic peptides or proteins, which are themselves prohibitively expensive and which would need to be delivered by catheters placed in the coronary arteries, further increasing the expense and difficulty of treatment.

It is clear from the above paragraph that the issue being addressed is the *cost* of the therapy to achieve the desired level of angiogenesis, not whether the therapy would work.

Additionally, the Applicants respectfully point out that claims 1-7 and 30-31 are drawn to compounds and pharmaceutical compositions, not methods of treatment. Particularly, with respect to the claimed molecules insofar as they are active by any route, they are enabled. More importantly, as noted above, the subject matter of bioavailability and pharmacokinetics have more to do with dose optimization and the cost of the dose rather than whether or not a drug or pharmaceutical composition actually works.

The field of the invention is pharmaceuticals. In this field, the level of skill is extremely high involving persons with advanced degrees and specialized knowledge and experience. And, in this field, the amount of experimentation that would be considered routine and not undue in drug formulation and screening is large. With respect to dose response in particular, the specification, as noted by the Examiner, describes some of the therapeutic objectives, bioavailability and pharmacokinetic factors to be addressed in determining an optimum dosage regimen. Indeed, the Federal Circuit has held that if a specification teaches one embodiment and sets forth a method for determining dose/response, the experimentation required to determine a dose/response curve is not undue, even if the studies proved to cost approximately $50,000 and took 6-12 months to accomplish. *United States v. Telectronics,* 8 USPQ2d 1217 (Fed. Cir. 1988).

In view of the amendments to the claims and the specification, the teachings in the related art, the guidance provided in the specification, and the field of art, Applicants believe that it would not require undue experimentation to practice the claimed subject matter and respectfully request that the above rejection be reconsidered and withdrawn.

Response to Rejection of Claims 1-4, 6-7, 28 and 29 as allegedly anticipated by Hall, et al. (U.S. Patent No. 6,387,663).

It is well settled that to anticipate a claim the reference must teach every element of the claim. (*see* MPEP §2131). Claim 1,as amended, recites the following:.

> A chimeric molecule comprising a peptide angiogenic factor covalently linked to a targeting peptide that specifically binds to a vascular endothelium.

The Action cited Hall as teaching a fusion protein comprising VEGF-B_{165} and a collagen binding domain. The Action further cited the collagen binding domain as von Willenbrand factor, which targets platelet aggregated to vascular lesions. The Hall patent describes von Willenbrand factor as specifically binding collagen (*see*, col. 6, line 27). In contrast, the present claims recite a targeting molecule that specifically binds to a

vascular endothelium. The term "vascular endothelium" is defined in the specification, at page 5, line 6, as meaning "a thin layer of flat epithelial cells that lines, for example, serous cavities, lymph vessels, and blood vessels."

In view of the above, Applicants respectfully request that the above rejection be reconsidered and withdrawn.

Claims 1-4, 6-7, 28 and 29 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Olson, et al., *International Journal of Cancer*, 73:865-70 (1997).

Olson, et al. disclose a VEGF-toxin conjugate in which the VEGF portion provides the targeting function. The Olson, et al. conjugate does not have a VEGF portion "linked to a targeting molecule that specifically binds to vascular endothelium." In fact, the toxin DT385 is not a targeting molecule. DT385 is a form of diphtheria toxin that lacks the receptor binding domain. See paragraph bridging pp. 865-866.

In view of the above, Applicants respectfully request that the above rejection be reconsidered and withdrawn.

Response to Rejection of Claims 1-4, 6-7, 28 and 29 as allegedly anticipated by Arora, et al., *Cancer Research*, 59:183-188, Abstract only (1999).

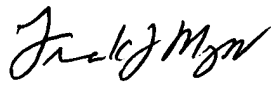
Aurora, el al. disclose a VEGF-toxin conjugate in which the VEGF portion provides the targeting function. The Aurora, et al. conjugate does not have a VEGF portion "linked to a targeting molecule that specifically binds to vascular endothelium." In fact, the toxin DT390 is not a targeting molecule. DT390 is a form of diphtheria toxin that lacks the receptor binding domain. See Aurora article provided with Supplemental Information Disclosure Statement, p. 183, first full paragraph in the right column.

In view of the above, Applicants respectfully request that the above rejection be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 925-472-5000 ext. 3012.

Respectfully submitted,



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This application is a divisional of, and claims the benefit of priority from, U.S. Patent Application Serial No. 09/327,045, filed June 7, 1999, abandoned, the full disclosure of which is incorporated herein by reference in its entirety.

Please replace the paragraph beginning at page 27, line 2, with the following rewritten paragraph:

Preferred targeting molecules of the invention comprise an amino acid sequence selected from the group comprising GGGVFWQ, HGRVRPH, VVLVTSS, CLHRGNSC, and CRSWNKADNRSC (SEQ ID NO:1-5, respectively) using the *in vivo* panning procedure described above and referenced below. The GGGVFWQ , HGRVRPH, VVLVTSS, and CLHRGNSC (SEQ ID NO:1-4, respectively) peptides selectively bind to normal cardiac endothelium. More specifically, the GGGVFWQ (SEQ ID NO:1) peptide showed a 5-fold enrichment to normal cardiac vasculature, while the HGRVRPH, VVLVTSS, CLHRGNSC (SEQ ID NO:2-4, respectively) peptides showed a 2-fold enrichment to normal cardiac vasculature. The CRSWNKADNRSC (SEQ ID NO:5) peptide showed 5-fold enrichment to ischemic myocardium. Details of how these peptides were identified and their properties are described in U.S.S.N. 09/326,718 [Campbell & Flores LLP Attorney Docket # P-LJ 3512] filed on even date herewith which is specifically incorporated herein by reference.

Please replace the paragraph beginning at page 48, line 25, with the following rewritten paragraph:

The plasmid pVEGF-Bwt167 is constructed by insertion of a 580bp PCR product derived from phage Lambda gt11-VEGF-Bwt167 into the expression plasmid pSI (Promega, Inc.). This phage is obtainable by screening a human fibrosarcoma cDNA library in lambda g11 (obtainable from Clontech, Inc.). The PCR reaction is performed employing the Advantage KlenTaq Polymerase Mix system (Clontech. Inc.) in a final volume of 100 microliter containing lng of the plasmid template, 0.5μM of primers P-wt167(l) 5'-GATCGCTAGC GGCAGCATGA GCCCTCTGCT CCGCCGCCTG-3' (SEQ ID NO:6) and P-wt167(2) 5'-TGACGCGGCC GCTCACCTTC GCAGCTTCCG GCACCTGCAG-3' (SEQ ID NO:7) as well as 0.2mM dNTPs, using the conditions 93°C 30 sec, 55°C 30 sec, 72°C 30

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Andrea L. Gashler, Reg. No. 41,029 (Depositor's name)

Andrea L. Gashler (Signature)

July 20, 2001 (Date)

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
09/326,718	06/07/99	027	DAVENPORT, A 1653	04/24/01

First Named Applicant: RUOSLAHTI, 35 USC 154(b) term ext. = 0 Days.

TITLE OF INVENTION: HEART HOMING PEPTIDES AND METHODS OF USING SAME

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 P-LJ-3512	514-012.000	F46	UTILITY	NO	$1240.00	07/24/01

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1 CAMPBELL & FLORES LLP
2
3

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(Authorized Signature) Andrea L. Gashler (Date) 7/20/01

Andrea L. Gashler, Reg. No. 41,029

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